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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,082	BRIEDEN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26-28* is/are allowed.

6)☒ Claim(s) *29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-8-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on [1] has been entered.

Claims 26-39 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 10-8-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 33-36 are drawn to "the recombinant vector of claim 26" lacking antecendent basis rendering the claims indefinite. Claim 26 is not drawn to "recombinant vector". Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide with SEQ ID NO:1 encoding an enzyme of SEQ ID NO:2 having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, does not reasonably provide enablement for any or all such polynucleotides from any source including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions (without any specific functions). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 29-39 are so broad as to encompass any polynucleotide encoding a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, from any source including those that are variants, mutants

or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since polynucleotides encode amino acid sequence of a protein that determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, (i.e., specific nucleotides in the polynucleotide) if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which nucleotides encoding specific amino acids can be modified and as well as the nucleotides required in order to make it encode the specific replacement amino acid in the original amino acid sequence based on the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single amidohydrolase. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides which encodes a variant polypeptide as well as polynucleotides with an undefined function/activity as in the case of a nucleotide sequence that simply hybridizes under stringent conditions (claim 31). The specification is limited to teaching the use of SEQ ID NO: 1 for encoding SEQ ID NO:2 but provides no guidance with regard to the making of variants and mutants or fragments of the same or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working

examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by these claims.

While recombinant and mutagenesis techniques are known, it would be an undue burden to those skilled in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all or any polynucleotide encoding a polypeptide with amidohydrolase activity including those that are variants, mutants or functional equivalents or fragments of said polynucleotide encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions because the specification does not establish: (A) regions of the polynucleotide encoding the protein structure which may be modified without affecting activity; (B) the general tolerance of amidohydrolase encoding polynucleotides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying specific

nucleotides (i.e., any amino acid residue) with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications in the sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the above rejection under 35 U.S.C. 112, 1st paragraph for lack of enablement, applicants have traversed the rejection arguing at length that claims are indeed enabled and that Examiner may have misunderstood the claims. In response, Examiner would like to reiterate, that there is no misunderstanding of the issue on part of the Examiner. Applicants have argued that Examiner's concerns and requirements for predictability appears to be unwarranted and misplaced and contrary to the power of mutagenesis as understood by the skilled in the art. Applicants appear to argue that because of the nature of the invention it is difficult to anticipate the structure of all functional variants. Applicants also appear to assume that claims are limited to variants made specifically by random mutagenesis. However, Examiner respectfully disagrees with such arguments as being persuasive to overcome the rejection. Claims in question are specifically drawn to any variant wherein any nucleotide from

the sequence is deleted, inserted or substituted. Such a claim is not limited to variants made only by random mutagenesis. Furthermore applicant's arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for making the specific amino acid changes in the encoded polypeptide followed by the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Hence the rejection is maintained.

Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules lacking the structure.

The specification does not contain any disclosure of the structure of all DNA sequences that encode a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, including those that are variants,

mutants or functional equivalents or fragments of said polynucleotide. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules lacking specific function.

The specification does not contain any disclosure of the function of all DNA sequences that simply hybridize to SEQ ID NO:1 under stringent hybridizing conditions. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different functions. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed

genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants have traversed the above rejection for lack of written description. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of Claims 29-30 includes species which are widely variant in structure. The genus Claims 29-30 is structurally

diverse and the genus of claims 31-39 are functionally diverse. As such, neither the description of the structure and function of SEQ ID NO:1 nor the disclosure of sole function present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Hence the above rejection is maintained.

Conclusion

Claims 26-28 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao. Ph.D.
January 31, 2005